It is also alleged that practicing the claimed methods would require undue experimentation because the claims encompass methods for decreasing OPG levels by anti-sense therapy and the specification does not enable anti-sense therapy. In support of this position, the Examiner has placed on the record a number of articles which allegedly support the view that use of anti-sense oligonucleotides in regulating levels of gene expression is unpredictable and the use of anti-sense oligonucleotides as a means of treating human diseases is also unpredictable. It is also argued that the specification provides no guidance regarding what portion of the OPG mRNA are effective target sequences, nor any guidance as to how anti-sense oligonucleotides should be administered and what conditions can be treated by such administration.

Applicants respectfully disagree with the claim construction offered by the Examiner. The Federal Circuit has clearly articulated that claims may be interpreted in light of the specification but that limitations appearing in the specification are not to be read into the claims *Intervet America, Inc. v. Kee-Vet Laboratories* 12 USPQ2d 1474 (Fed. Cir., 1989). Claim 49 recites a method of regulating levels of OPG in an animal and the practice of such method is not, nor is it required to be, limited to any particular purpose. In the present case, Applicants have shown that increasing levels of OPG in mice leads to increased bone density and indicates a therapeutic use for OPG of treating bone disease (see Example 3 of the specification). However, there is nothing in the specification that would suggest or imply that regulation of OPG expression is carried out for the sole purpose of treating bone disease. In fact, the specification suggests otherwise at p. 12, starting on line 26:

> The nucleic acids are also used for the development of transgenic animals which may be used for the production of the polypeptide ... .

Thus one skilled in the art would appreciate that OPG levels may be regulated in order to produce sufficient quantities of the polypeptide for a variety of reasons which may or may not be explicitly disclosed in the application but which may be readily ascertained by one skilled in the art.

Even assuming for the sake of argument that the Examiner's claim construction is correct, Applicants maintain that the subject matter as construed by the Examiner is enabled in view of the results presented in the specification showing an increase in bone density when levels of OPG are increased in transgenic mice. The Examiner has previously argued that the use of OPG gene therapy for the treatment of bone diseases was not enabled by virtue of an asserted lack of predictability in applying gene therapy. Applicants will not review those arguments in the present response. However, the Examiner has failed to explain why one skilled in the art, using the teachings of the specification, would not be able to extrapolate without undue experimentation the claimed method of regulating OPG expression to the treatment of bone diseases. The issue of alleged prior failures of gene therapy to treat diseases other than bone diseases, which has been relied upon by the Examiner in previous Office Actions, is simply not relevant regardless of how the claims are construed.

As to the Examiner's arguments that anti-sense therapy requires undue experimentation, Applicants respectfully traverse the rejection. The Examiner has failed to show that it would require undue experimentation to carry out the invention as a whole, or to carry out an anti-sense aspect of the invention. In the first instance, the Examiner seems to argue that because anti-sense regulation of OPG expression is not enabled, then regulation of OPG expression by any method is not enabled. Applicants are not aware of any Federal Circuit decision requiring that each and every mode of carrying out the invention be enabled in order to satisfy the enablement requirement. To the contrary, the Federal Circuit has held that "[t]he enablement requirement is met if the description enables any mode of making and using the invention". *Engel Indus., Inc. v. Lockformer Co.* 20 USPQ2d 1300, 1304 (Fed. Cir. 1991). See also *Johns Hopkins University v. Cellpro Inc.* 47 USPQ2d 1719 (Fed. Cir. 1998) wherein the Federal Circuit rejected arguments that claims to CD34 antibodies were not enabled because some of the immunogens disclosed in the application allegedly failed to elicit the claimed antibodies. In the present case, Applicants have enabled a method of regulating OPG expression in Example 3 and any allegation that anti-sense regulation is not enabled is legally irrelevant to enablement of the claimed invention as a whole.

Furthermore, the Examiner has not established that anti-sense regulation of gene expression in general, and OPG expression in particular, would require undue experimentation. The criteria for determining whether experimentation is undue has been set forth in *In re Wands* 8 USPQ2d 1400, 1403-1407 (Fed. Cir. 1988). The test for undue experimentation is not quantitative if it is merely routine to one skilled in the art, or if the specification provides guidance with respect to the direction in which the experimentation should proceed in order to practice an embodiment of the claimed invention. *PPG Indus., Inc. v. Guardian Indus. Corp.* 37 USPQ2d 1618, 1623 (Fed. Cir. 1996).

In the present Office Action, the Examiner has cited publications by Milligan et al. (J Med Chem 36: 1923-1937 (1993)), Hoke et al. (U.S. Patent No. 5,585,479), Westermann et al. (Biomed Biochim Acta 48: 85-93 (1989)) and Bennett (Science 271: 434 (1996)) alleging that anti-sense regulation of gene expression is unpredictable and thus would require undue experimentation. Significantly, every one of these articles either demonstrates or refers to positive experimental results for regulating the expression of a gene using anti-sense oligonucleotides. For example, the Bennett article, in footnote 1, cites eleven articles which show anti-sense gene regulation in vitro and in vivo. Applicants are puzzled as to how the Examiner can assert undue experimentation in view of reports by a number of groups showing that anti-sense gene regulation can be achieved. Applicants submit that regulation of OPG expression by anti-sense is enabled by the teachings of the specification combined with routine experimentation. Although it is argued that a particular site on OPG mRNA for anti-sense regulation has not been specified nor is one apparent based on the specification, there is no evidence provided that finding such a site and preparing the appropriate anti-sense oligonucleotide would not be routine and reasonable experimentation. Indeed, given the number of successful reports of anti-sense regulation of a variety of different genes, it would not involve an undue effort to prepare anti-sense oligonucleotides and test various sites on OPG mRNA for regulation of expression.

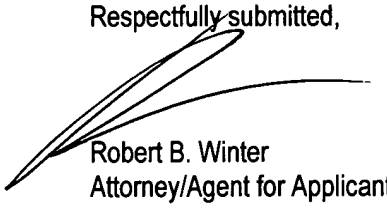
The Examiner further argues that there is considerable unpredictability in developing anti-sense oligonucleotides as therapeutics and argues that the path from in vitro activity to practical therapeutic application is not straightforward or routine. The Examiner has cited the Stein et al. (Science 261: 1004-1012 (1993)), Wagner (Nature 372: 333-335 (1994)), Stull et al. (Pharmaceutical Research 12: 465-483 (1995)), Wu-Pong (Pharmaceutical Technology 118: 102-114 (1994)), Miller et al. (Parasitology Today 10: 92-97 (1994)) and Rojanasakul (Advanced Drug Delivery Reviews 18: 115-131 (1996)) to highlight the progress that is required in order to use anti-sense as a therapeutic. This argument is contrary to the Examiner's own references which clearly show regulation of gene expression by anti-sense oligonucleotides in vitro and in cell culture. In addition, some of the references refer to anti-sense therapies which have already progressed into human clinical trails (see Wu-Pong, p. 110 and Rojanasakul, p.126 for example), suggesting a very strong correlation between results shown in vitro and in cell culture and the use of anti-sense oligonucleotides as therapeutics. Moreover, arguments of alleged lack of enablement of anti-sense regulation do not render the claimed invention as a whole nonenabled as Applicants have already shown in vivo regulation of OPG expression by a method other than anti-sense. Thus the claimed invention is fully enabled.

The Examiner also argues that the specification lacks specific guidance, particularly with respect to what portions of OPG mRNA are target sequences and how antisense oligonucleotides should be administered. Applicants point out that the application provides specific guidance in Example 3 on regulating OPG expression in vivo and that guidance together with routine experimentation would fully enable one to practice the full scope of the claimed invention. It is respectfully requested that the rejection be withdrawn.

## CONCLUSION

In view of the remarks set forth above, Claims 49-53 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,



Robert B. Winter
Attorney/Agent for Applicant(s)
Registration No.: 34,458
Phone: (805) 447-2425
Date: March 7, 2000

Please send all future correspondence to:

U.S. Patent Operations/RBW
Dept. 430, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799